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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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RAMIREZ, DELIA M

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1652

DATE MAILED: 06/18/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/432,503 | CECH ET AL. |
| | Examiner | Art Unit |
| | Delia M. Ramirez | 1652 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION:

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 April 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 41-88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 41-47,50,51,56 and 58-88 is/are rejected.
- 7) Claim(s) 48,49,52-55 and 57 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>24</u> . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Status of the Application

Claims 41-88 are pending.

Applicant's amendment of claims 41, 43, 44, 47, 50, 51, 53, 56, 57, in Paper No. 22, filed on 3/3/2003 is acknowledged.

Applicant's amendment of claim 41 and addition of claims 58-88 in Paper No. 25, filed on 4/22/2003 is acknowledged.

Applicant's submission of a declaration under 37 CFR 1.132 by Calvin Harley and John Irving on 3/3/2003 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 3/3/2003 is acknowledged. Reference CO has not been considered since no date has been provided. The remainder of the submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

2. Applicants submit in Paper No. 22, filed on 3/3/2002 that formal drawings are being forwarded under separate cover. It is noted that the Examiner is unable to locate such drawings in the file and the PTO has no record of a separate submission of formal drawings. Therefore,

the drawings remain objected under 37 CFR 1.84 or 1.152. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 43-44, 47, 50-51, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 43, 47, 50 and 56 (claims 44, 51 dependent thereon) are indefinite in the recitation of “the method of.....further comprising selecting the cell from other cells because it expresses increased telomerase catalytic activity as a result of introducing the polynucleotide” as it is unclear and confusing. The term “the cell from other cells” is confusing since it is unclear as to which cells are being referred to. It is suggested that the term be amended to recite “further comprising selecting a cell which expresses an increased level of telomerase catalytic activity as a result of introducing the polynucleotide. For examination purposes, the suggested language will be used. Correction is required.

6. Claims 43, 47, 50 and 56 were previously rejected under 35 USC 112, second paragraph. Applicants assert that the claims have been amended to obviate the previous rejection. It is noted however that the amendment is not deemed sufficient to overcome the rejection for the reasons set forth above.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 66, 69, 70, 74, 77, 78, 82, 85, and 86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 66, 74 and 82 are directed to the methods of claim 62, 63, or 64 wherein the cell is a fibroblast of the skin. Claims 69, 77 and 85 are directed to the methods of claim 62, 63 or 64 wherein the cell is an endothelial cell. Claims 70, 78, and 86 are directed to the methods of claims 62, 63, or 64 wherein the cell is a retinal pigmented epithelial cell of the eye. The Examiner has been unable to locate support for “a fibroblast of the skin”, “endothelial cell”, and “retinal pigmented epithelial cell of the eye”. Thus, there is no indication that the methods of claims 62, 63 or 64 wherein the cell is a fibroblast of the skin, an endothelial cell or a retinal pigmented epithelial cell of the eye, were within the scope of the invention as conceived by

Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

9. Claims 58-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 58-88 are directed to a method of increasing the proliferative capacity of a mammalian cell in vivo by introducing in said cell a genus of polynucleotides encoding a telomerase reverse transcriptase protein, variant or fragment having telomerase catalytic activity when complexed with telomerase RNA, wherein said polynucleotides hybridize to the polynucleotide of SEQ ID NO: 1 under the conditions as specified in the claims, and wherein the introduction of the genus of polynucleotides is achieved by any means. While the specification discloses a method of increasing the proliferative capacity and the production of immortalized cells, cell lines and animals as one of the preferred embodiments of the invention (page 118, line 24, page 120, line 19), there is no evidence or examples provided in the specification which show that introduction of a polynucleotide encoding a telomerase reverse transcriptase to a mammalian cell in vivo results in increased proliferative capacity. Furthermore, there is no disclosure of all methods of introducing a polynucleotide to a subject in vivo. It is noted that the only example provided in the specification (Example 2, page 224-225) relates to the transformation of several cell lines in vitro with a polynucleotide encoding human

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telomerase reverse transcriptase (hTRT). Example 2 only discloses that mRNA levels of hTRT in mortal cells is lower than that of immortal cells.

While one could argue that the claimed method is adequately described in view of the information provided by the specification and the expectation that *in vitro* results can be extrapolated *in vivo*, those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, the greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit extrapolation of *in vitro* assays to *in vivo* conditions with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived (page. 4, Major Differences *In Vitro*). The information provided by the specification is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed

method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

10. Claims 58-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the proliferative capacity of a mammalian cell in vitro by transforming said cell with a polynucleotide encoding a telomerase reverse transcriptase protein, variant or fragment having telomerase catalytic activity when complexed with telomerase RNA, wherein said polynucleotide hybridizes to the polynucleotide of SEQ ID NO: 1 under the conditions as specified in the claims, does not reasonably provide enablement for said method in vivo using any method to introduce the polynucleotide in the mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

11. This rejection has been discussed at length in Paper No. 17, mailed on 8/26/02 and is applied to newly added claims 58-88 for the reasons of record.

12. Applicants argue that the Office Action provides no basis for asserting that the claimed invention would not work *in vivo*. Applicants submit that working examples are not required for the specification to be enabling for the claimed invention. Applicants argue that the analysis of whether the specification is enabling for the claimed invention requires two questions: (1) what is enabled by the specification and (2) do the embodiments that are enabled by the specification meet the limitations of what is being claimed?. According to Applicants, the hTRT vectors described in the specification have been proven to increase proliferative capacity in cultured cells

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and there is a priori evidence that the vectors that cause hTRT expression in vitro since many of these vectors have been proven to cause expression of other genes in vivo. Applicants submit a list of references published after the priority date claimed to support their position. In addition, Applicants have submitted two declarations by Dr. Calvin Harley and Dr. John Irving, both employees of Geron Corporation, the assignee of record for the instant application. According to Applicants, Dr. Harley provides affirmative evidence that hTRT expression can be used in vivo with important therapeutic effects. In regard to Dr. Irving's declaration, Applicants assert that as an expert in the field of vector biology, Dr Irving indicates that one of ordinary skill in the art would have the ability to make telomerase vectors capable of increasing proliferative capacity in vivo using the information provided by the instant application, in particular, the use of adenovirus vectors, which are the same vectors used in the ischemic ear wound experiment mentioned in Dr. Harley's declaration. It is Applicant's contention that the specification, in combination with common practice in the relevant art at the time of filing, enables one of skill in the art to make effective vectors for causing expression of hTRT in cells without undue experimentation. In addition, Applicants conclude that a number of clinical trials have shown promising results for expressing other genes using vectors such as adenoviruses, retroviruses, and AAV, validating the use of such vectors for gene expression in vivo.

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejections as it applies to newly added claims 58-88. The instant claims are drawn to a method of increasing proliferative capacity in vivo by introducing a polynucleotide encoding telomerase reverse transcriptase in a mammalian cell by any means. It is acknowledged that working examples are not required for the specification to be enabling for the claimed invention.

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However, in the instant case, one of skill in the art cannot reasonably conclude that in vitro results can be extrapolated to in vivo conditions since, as discussed at length above, it is well known in the art that in vitro assays and/or cell-cultured based assays, while generally useful to observe basic physiological and cellular phenomenon, cannot be used with a reasonable degree of predictability in vivo due to the greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in vitro assay. See the teachings of Freshney already discussed. Furthermore, it is unclear as to how one can be enabled to practice the claimed method using any means of delivery of the polynucleotide when as known in the art, only certain vectors have been shown to be useful in the delivery of polynucleotides in vivo.

In regard to the declaration by Dr. Harley, it is noted that the reference by Rudolph et al. and U.S. Application No. 10/143,536, both of which deal with the delivery of a polynucleotide encoding hTRT and its expression in vivo, have been considered but they are not deemed sufficient to overcome the enablement rejection as it relates to the claimed method in vivo since neither Rudolph et al. nor U.S. Application No. 10/143,536 can establish enablement of the current claims at the time the invention was filed (11/2/1999). Rudolph et al. was published in February 18, 2000 whereas U.S. Application No. 10/143,536 was filed on 05/13/2002.

In regard to the declaration by Dr. Irving, while it is agreed that adenovirus and retrovirus vectors were known at the time the invention was made and the use of such vectors for gene therapy was suggested at the time the invention was made, no evidence is presented in the specification that once the hTRT polynucleotide is delivered to a subject using any delivery method or even adenovirus/retrovirus vectors, proliferative capacity of the target cell is achieved

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in vivo. The Examiner acknowledges Dr. Irving's declaration in regard to the construction of an hTRT adenovirus vector in U.S. Application No. 10/143,536, however, as indicated above, the information disclosed in such application is not deemed sufficient to overcome the enablement rejection for the reasons set forth above.

In regard to arguments as to the expectation of successfully practicing the claimed method in vivo, it is not the Examiner's contention that adenovirus or retrovirus vectors could not be used to introduce recombinant DNA in a mammalian subject (in vivo) at the time of filing. However, the Examiner disagrees with Applicant's contention that since these vectors have been used to express recombinant DNA in vivo, one of skill in the art at the time of filing should have expected increased proliferation of a target cell in vivo if a polynucleotide encoding telomerase reverse transcriptase was delivered to a subject. It is noted that, with the exception of a reference by Bramson et al. (1995), most of the examples provided as footnote 2 in page 5 were published after the priority date claimed or the filing date. At best, one of skill in the art would have concluded that adenovirus or retrovirus vectors could be used to deliver recombinant DNA to a mammalian subject. Therefore, in view of the evidence provided, the teachings of the specification and the state of the art at the time the invention was made, one cannot reasonably conclude that the claimed in vivo method is fully enabled by the specification.

Double Patenting

14. Claims 41-47 and 58-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-8 of U.S. Patent No. 6337200.

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15. This rejection, which has been discussed at length in Paper No. 17, mailed on 8/26/2002, was applied to claims 41-47 and is now applied to newly added claims 58-60 for the reasons of record.

16. Applicants agree that the subject matter claimed in the current application covers functionally active variants of hTRT however they contend that obviousness-type double patenting is not applicable in the instant case since the disclosure of the present application was first filed on November 19, 1997 whereas U.S. Patent No. 6337200 has an effective filing date of August 3, 1998. Applicants argue that the variants hTRT described in U.S. Patent No. 6337200 were not found obvious over the instant application, therefore the subject matter of the issued patent is not obvious with respect to the present application. Applicants submit that since the present disclosure has an earlier filing date, it could not be challenged as obvious over the 6337200 patent if that patent was filed by another party. Furthermore, Applicants argue that under the new 20-year provisions of 35 USC 154(a)(2), no extension of patent term results from issuance of a patent on the present application. Therefore, it is Applicant's contention that it would be unfair to require Applicants to file a terminal disclaimer with respect to a later-filed patent just because the later-filed patent is their own.

17. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. According to PTO records, the instant application was filed on 11/2/1999 and it is a continuation in part (CIP) of U.S. Application No. 08/915,503, filed on 8/14/1997. While it is agreed that the variants disclosed in U.S. Patent No. 6337200 were not disclosed in the instant application, as acknowledged by Applicants, the subject matter of the instant claims encompasses the subject matter of claims 7-8 of U.S. Patent No. 6337200. As

indicated in previous Office Action Paper No. 17, the obviousness type double patenting rejection is applied in view of the fact that the claims in the instant application are generic to all that is recited in claims 7-8 of U.S. Patent No. 6337200. Amended claims 41-47 are now directed to a method of increasing proliferative capacity of a mammalian cell in vitro with a polynucleotide which encodes a telomerase reverse transcriptase or variant thereof, wherein said polynucleotide hybridizes under specific hybridization conditions to the polynucleotide of SEQ ID NO: 1. Newly added claims 58-60 are drawn to a method of increasing proliferative capacity of a mammalian cell in vivo and in vitro with a polynucleotide which encodes a telomerase reverse transcriptase or variant thereof, wherein said polynucleotide hybridizes under specific conditions to the polynucleotide of SEQ ID NO: 1. Claims 7-8 of U.S. Patent No. 6337200 are drawn to a method of increasing the proliferative capacity of a human cell in vitro wherein a polynucleotide encoding a variant of the human telomerase reverse transcriptase of SEQ ID NO: 2 having processive catalytic activity, wherein the variant has a deletion of at least 10 amino acids from specified regions of the polypeptide of SEQ ID NO: 2. The polynucleotides encoding the variants of claims 7-8 will hybridize to the polynucleotide of SEQ ID NO: 1 under the conditions recited in the claims. Therefore, claims 7-8 of U.S. Patent No. 6337200 fall within the scope of claims 41-47 and 58-60 of the instant application as written.

In regard to arguments that requesting Applicants to file a terminal disclaimer is improper and unfair in view of the filing dates of the instant application and U.S. Patent No. 6337200, this is not found persuasive. While it is agreed that under the new 20-year term provisions, no patent extension results from issuance of a patent on the present application if the effective filing date is earlier than that of U.S. Patent No. 6337200, it is noted that filing a terminal disclaimer not only

ensures that the term for a patent granted on the examined application will not extend past the expiration of the term of the conflicting patent but it also ensures that the patent granted on the examined application is enforceable only as long as the patent granted on the examined application and the conflicting patent are commonly owned. It is also noted that in the analysis of obviousness type double patenting, the Examiner applied the one-way obviousness test since there is no evidence in PTO records of administrative delay in the examination of the instant application. As such, even if the instant application has an earlier effective filing date than that of U.S. Patent No. 6337200, according to the one-way obviousness test, the method of claims 7-8 of U.S. Patent No. 6337200 is encompassed by claims 41-47 and 58-60 of the instant application. As such, the double patenting rejection applied is deemed proper and is maintained.

Allowable Subject Matter

18. Claims 48-49, 52-55 and 57 appear to be allowable over the prior art of record but are objected to since they depend upon rejected claims.

Conclusion

19. No claim is in condition for allowance.

20. Applicant's amendment of claims 41, 43, 44, 47, 50, 51, 53, 56, 57 and addition of claims 58-88, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

22. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

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June 10, 2003